REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES

Julie R. Ingelfinger, M.D., *Editor*

Physiological Approach to Assessment of Acid–Base Disturbances

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Internal acid–base homeostasis is fundamental for maintaining life. Accurate and timely interpretation of an acid–base disorder can be lifesaving, but the establishment of a correct diagnosis may be challenging.[1] The three major methods of quantifying acid–base disorders are the physiological approach, the base-excess approach, and the physicochemical approach (also called the Stewart method).[2] This article reviews a stepwise method for the physiological approach.

The physiological approach uses the carbonic acid–bicarbonate buffer system. Based on the isohydric principle, this system characterizes acids as hydrogen-ion donors and bases as hydrogen-ion acceptors. The carbonic acid–bicarbonate system is important in maintaining homeostatic control. In the physiological approach, a primary change in the partial pressure of carbon dioxide (P_{CO_2}) causes a secondary "adaptive" response in the bicarbonate concentration and vice versa; further changes in carbon dioxide or bicarbonate reflect additional changes in acid–base status. The four recognized primary acid–base disorders comprise two metabolic disorders (acidosis and alkalosis) and two respiratory disorders (acidosis and alkalosis).

The hydrogen-ion concentration is tightly regulated because changes in hydrogen ions alter virtually all protein and membrane functions.[2-6] Since the concentration of hydrogen ions in plasma is normally very low (approximately 40 nmol per liter), the pH, which is the negative logarithm of the hydrogen-ion concentration, is generally used in clinical medicine to indicate acid–base status.[3-5,7] The terms "acidemia" and "alkalemia" refer to states in which the blood pH is abnormally low (acidic) or abnormally high (alkaline). The process in which the hydrogen-ion concentration is increased is called acidosis, and the process in which the hydrogen-ion concentration is decreased is called alkalosis.[3,4] The traditional determination of acid–base values is based on the Henderson–Hasselbalch equation (in which pK denotes the acid dissociation constant):

$$pH = pK + \log_{10}(\text{bicarbonate } [HCO_3^-] \div [0.03 \times \text{partial pressure of arterial carbon dioxide } (P_{aCO_2})]),$$

where bicarbonate is in millimoles per liter and P_{aCO_2} is in millimeters of mercury.[6,7] An acid–base disorder is called "respiratory" when it is caused by a primary abnormality in respiratory function (i.e., a change in the P_{aCO_2}) and "metabolic" when the primary change is attributed to a variation in the bicarbonate concentration.

HISTORY AND PHYSICAL EXAMINATION

The first step in assessment of an acid–base disorder is a careful clinical evaluation. Various signs and symptoms often provide clues regarding the underlying acid–base disorder; these include the patient's vital signs (which may indicate shock or

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sepsis), neurologic state (consciousness vs. unconsciousness), signs of infection (e.g., fever), pulmonary status (respiratory rate and presence or absence of Kussmaul respiration, cyanosis, and clubbing of the fingers), and gastrointestinal symptoms (vomiting and diarrhea). Certain underlying medical conditions such as pregnancy, diabetes, and heart, lung, liver, and kidney disease may also hint at the cause. The clinician should determine whether the patient has taken any medications that affect acid–base balance (e.g., laxatives, diuretics, topiramate, or metformin) and should consider signs of intoxication that may be associated with acid–base disturbances (e.g., acetone fetor as a sign of diabetic ketoacidosis or isopropyl alcohol intoxication, and visual disturbance as a symptom of methanol intoxication).

DETERMINATION OF THE PRIMARY ACID–BASE DISORDER AND THE SECONDARY RESPONSE

The second step is to determine the primary acid–base disorder and the secondary response. The range of pH that is compatible with life is 7.80 to 6.80 (a hydrogen-ion concentration [H^+] of 16 to 160 nmol per liter).[3] For the purposes of this review, the reference value for pH is 7.40±0.02, for $Paco_2$, 38±2 mm Hg, and for [HCO_3^-], 24±2 mmol per liter. The four major acid–base disturbances are defined as primary acid–base disorders (Table 1 and Fig. 1). Empirical observations suggest that the homeostatic response to acid–base disorders is predictable and can be calculated.[9-18] In response to metabolic acid–base disturbances, changes in the respiratory rate develop quickly, and a new steady-state $Paco_2$ is reached within hours. In cases of persistent respiratory abnormalities, metabolic compensation develops slowly, and 2 to 5 days are required for the plasma bicarbonate concentration to reach a new steady-state level. A respiratory change is called "acute" or "chronic" depending on whether a secondary change in the bicarbonate concentration meets certain criteria (Table 1). Mixed acid–base disorders are diagnosed when the secondary response differs from that which would be expected.[13,18-23]

There are several caveats concerning compensatory changes. Blood gas values can always be explained by two or more coexisting acid–base disorders.[12] The current prediction equations that are used to assess acid–base status are approximations based on nearly 40-year-old studies involving humans and dogs.[1] Experimental studies of severe chronic hypocapnia and hypercapnia in humans are not ethically feasible; thus, data are insufficient to construct confidence limits for

Table 1. Primary Acid–Base Disturbances with a Secondary ("Compensatory") Response.*

Metabolic acidosis
pH <7.38 and bicarbonate [HCO_3^-] <22 mmol per liter
Secondary (respiratory) response: $Paco_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$ mm Hg† or $[HCO_3^-] + 15$ mm Hg‡
Complete secondary adaptive response within 12–24 hr
Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $Paco_2$ is greater or less than predicted
Metabolic alkalosis
pH >7.42 and [HCO_3^-] >26 mmol per liter
Secondary (respiratory) response: $Paco_2 = 0.7 \times ([HCO_3^-] - 24) + 40 \pm 2$ mm Hg or $[HCO_3^-] + 15$ mm Hg‡ or $0.7 \times [HCO_3^-] + 20$ mm Hg§
Complete secondary adaptive response within 24–36 hr
Superimposed respiratory acidosis or alkalosis may be diagnosed if the calculated $Paco_2$ is greater or less than predicted
Respiratory acidosis
pH <7.38 and $Paco_2$ >42 mm Hg
Secondary (metabolic) response
Acute: [HCO_3^-] is increased by 1 mmol/liter for each $Paco_2$ increase of 10 mm Hg above 40 mm Hg
Chronic: generally [HCO_3^-] is increased by 4–5 mmol/liter for each $Paco_2$ increase of 10 mm Hg above 40 mm Hg
Complete secondary adaptive response within 2–5 days
Superimposed metabolic alkalosis or acidosis may be diagnosed if the calculated [HCO_3^-] is greater or less than predicted
Respiratory alkalosis
pH >7.42 and $Paco_2$ <38 mm Hg
Secondary (metabolic) response
Acute: [HCO_3^-] is decreased by 2 mmol/liter for each $Paco_2$ decrease of 10 mm Hg below 40 mm Hg
Chronic: [HCO_3^-] is decreased by 4–5 mmol/liter for each $Paco_2$ decrease of 10 mm Hg below 40 mm Hg
Complete secondary adaptive response in 2–5 days
Superimposed metabolic alkalosis or acidosis may be diagnosed if the calculated [HCO_3^-] is greater or less than predicted

* Reference values for arterial blood gases are the following: pH, 7.4±0.02, partial pressure of arterial carbon dioxide ($Paco_2$), 40±2 mm Hg, and bicarbonate, 24±2 mmol per liter. Reference values for venous blood gases are the following: pH, 7.36 to 7.38, $Pvco_2$, 43 to 48 mm Hg, and bicarbonate, 25 to 26 mmol per liter. To convert the values for Pco_2 to kilopascals, divide by 7.5006.
† This formula is also known as the Winters formula.
‡ These calculations are easy to make at the bedside but are not reliable at all bicarbonate concentrations. Data are from Berend.[8]
§ The secondary respiratory response is difficult to predict in metabolic alkalosis.

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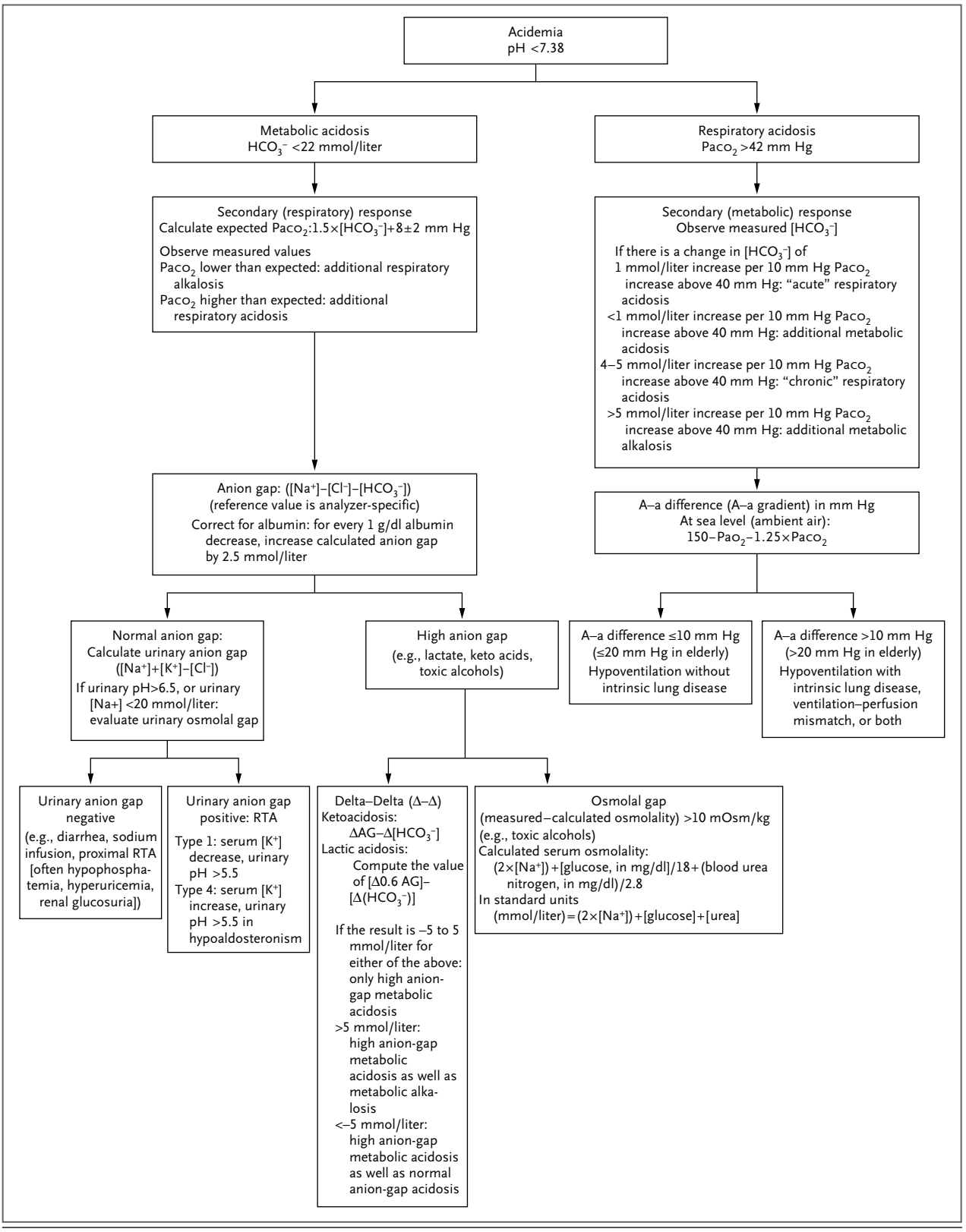
Acidemia
pH <7.38
Metabolic acidosis
HCO_3^- <22 mmol/liter
Respiratory acidosis
$Paco_2$ >42 mm Hg
Secondary (respiratory) response
Calculate expected $Paco_2$:1.5×[HCO_3^-]+8±2 mm Hg
Observe measured values
$Paco_2$ lower than expected: additional respiratory alkalosis
$Paco_2$ higher than expected: additional respiratory acidosis
Secondary (metabolic) response
Observe measured [HCO_3^-]
If there is a change in [HCO_3^-] of
1 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: "acute" respiratory acidosis
<1 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: additional metabolic acidosis
4–5 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: "chronic" respiratory acidosis
>5 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: additional metabolic alkalosis
Anion gap: ([Na^+]–[Cl^-]–[HCO_3^-])
(reference value is analyzer-specific)
Correct for albumin: for every 1 g/dl albumin decrease, increase calculated anion gap by 2.5 mmol/liter
A–a difference (A–a gradient) in mm Hg
At sea level (ambient air):
150–Pao_2–1.25×$Paco_2$
Normal anion gap:
Calculate urinary anion gap ([Na^+]+[K^+]–[Cl^-])
If urinary pH>6.5, or urinary [Na+] <20 mmol/liter: evaluate urinary osmolal gap
High anion gap
(e.g., lactate, keto acids, toxic alcohols)
A–a difference ≤10 mm Hg (≤20 mm Hg in elderly)
Hypoventilation without intrinsic lung disease
A–a difference >10 mm Hg (>20 mm Hg in elderly)
Hypoventilation with intrinsic lung disease, ventilation–perfusion mismatch, or both
Urinary anion gap negative
(e.g., diarrhea, sodium infusion, proximal RTA [often hypophosphatemia, hyperuricemia, renal glucosuria])
Urinary anion gap positive: RTA
Type 1: serum [K^+] decrease, urinary pH >5.5
Type 4: serum [K^+] increase, urinary pH >5.5 in hypoaldosteronism
Delta–Delta (Δ–Δ)
Ketoacidosis:
ΔAG–Δ[HCO_3^-]
Lactic acidosis:
Compute the value of [Δ0.6 AG]–[Δ(HCO_3^-)]
If the result is –5 to 5 mmol/liter for either of the above: only high anion-gap metabolic acidosis
>5 mmol/liter: high anion-gap metabolic acidosis as well as metabolic alkalosis
<–5 mmol/liter: high anion-gap metabolic acidosis as well as normal anion-gap acidosis
Osmolal gap
(measured–calculated osmolality) >10 mOsm/kg
(e.g., toxic alcohols)
Calculated serum osmolality:
(2×[Na^+])+[glucose, in mg/dl]/18+(blood urea nitrogen, in mg/dl)/2.8
In standard units
(mmol/liter)=(2×[Na^+])+[glucose]+[urea]

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Figure 1. Assessment of Acidosis.

Reference values for the alveolar–arterial (A–a) oxygen tension difference are less than 10 mm Hg in young persons and less than 20 mm Hg in the elderly. ΔAG denotes delta anion gap, $Paco_2$ partial pressure of arterial carbon dioxide (mm Hg), Pao_2 partial pressure of arterial oxygen (mm Hg), and RTA renal tubular acidosis. To convert the values for $Paco_2$, Pao_2, and the alveolar–arterial difference to kilopascals, multiply by 0.1333.

severe chronic respiratory alkalosis and acidosis. It is generally accepted that compensatory processes may normalize the pH only in chronic respiratory alkalosis. In contrast with older data, data from a more recent study[13] indicate that the pH in chronic respiratory acidosis may be normal and, in individual cases, higher than generally recognized (pH >7.40).[13,17,24] Furthermore, the usual compensatory changes in the $Paco_2$ may be limited in cases of severe hypoxemia. Instruments used for the measurement of blood gas and electrolytes may differ, affecting results.[25-27] Indeed, studies involving the use of modern analyzers show pH reference values (7.40 to 7.44)[28-30] and secondary responses that differ from those published in textbooks.[12,21,31] Although these differences are small, a reappraisal of the prediction equations may be needed.

EVALUATION OF THE METABOLIC COMPONENT OF AN ACID–BASE DISORDER

The third step in an evaluation is to consider the metabolic component of the acid–base disorder.

METABOLIC ACIDOSIS

Calculation of the anion gap is useful in the initial evaluation of metabolic acidosis.[32-45] The sum of the positive and negative ion charges in plasma are equal in vivo: $[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]+[H^+]+$unmeasured cations$=[Cl^-]+[HCO_3^-]+[CO_3^{2-}]+[OH^-]+$albumin$+$phosphate$+$sulfate$+$lactate$+$unmeasured anions (e.g., inorganic anions).[35-44] Routine measurement of all the ions in plasma is generally unnecessary. A more practical approach takes advantage of the fact that most plasma ions are normally present at relatively low concentrations and that variations into the pathologic range are quantitatively small. The three ions with the highest plasma concentrations and largest variations in concentration are used to calculate the excess of "unmeasured anions" in metabolic acidosis that constitutes the "anion gap," which is calculated as $[Na^+]-[Cl^-]-[HCO_3^-]$.

A true ion gap, however, does not exist in vivo, because the sum of the positive and negative ion charges in plasma must be equal. Wide reference ranges of 3.0 to 12.0 mmol per liter up to 8.5 to 15.0 mmol per liter in the anion gap have been reported,[33-36,43] owing to differences in laboratory methods.[23,45] Consequently, clinicians should know the reference range for their own laboratory.

High-Anion-Gap Metabolic Acidosis

There are many causes of high anion-gap metabolic acidosis (Table 2). A useful mnemonic for the most common causes is GOLD MARRK (glycols [ethylene and propylene], 5-oxoproline [pyroglutamic acid], L-lactate, D-lactate, methanol, aspirin, renal failure, rhabdomyolysis, and ketoacidosis).[46] The anion gap increases when the concentration of bicarbonate decreases relative to levels of sodium and chloride because of overproduction of acid (in ketoacidosis, lactic acidosis, and drug and alcohol-related intoxication), underexcretion of acid (in advanced renal failure), cell lysis (in massive rhabdomyolysis), or other circumstances (e.g., the use of penicillin-derived antibiotics).

Uses and Limitations of the Anion Gap

Lactic acidosis accounts for about half the cases of a high anion gap[33-49] and is often due to shock or tissue hypoxia.[44,47] However, the anion gap is a relatively insensitive reflection of lactic acidosis — roughly half the patients with serum lactate levels between 3.0 and 5.0 mmol per liter have an anion gap within the reference range.[39,40] The anion gap, which has a sensitivity and specificity below 80% in identifying elevated lactate levels, cannot replace a measurement of the serum lactate level.[39,40,47-50] Nevertheless, lactate levels are not routinely measured or always rapidly available, and a high anion gap can alert the physician that further evaluation is necessary.[34,39,43] Unfortunately, a baseline value of the anion gap is generally not available for an individual patient. In addition, the anion gap should always be adjusted for the albumin concentration, because this

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Table 2. The Anion Gap in Relation to Common Medical Conditions with Metabolic Acidosis.*

High anion gap
Overproduction of acid
Ketoacidosis (diabetic ketoacidosis, alcoholic ketoacidosis, starvation)
Lactic acidosis
L-Lactic acidosis
Type A — hypoxic (septic shock, mesenteric ischemia, hypoxemia, hypovolemic shock, carbon monoxide poisoning, cyanide)
Type B — nonhypoxic (thiamine deficiency, seizure, medications [nonnucleoside reverse-transcriptase inhibitors, metformin, propofol, niacin, isoniazid, iron], intoxication [salicylate, ethylene glycol, propylene glycol, methanol, toluene ingestion (early), paraldehyde])
D-Lactic acidosis in the short-bowel syndrome
Underexcretion of acid (advanced renal failure)†
Impaired lactate clearance in liver failure (also type B acidosis)
Cell lysis (massive rhabdomyolysis)
Use of penicillin-derived antibiotics
Pyroglutamic acid (5-oxoproline)[32]
Normal anion gap
Loss of bicarbonate
Gastrointestinal conditions (diarrhea, ureteral diversions, biliary or pancreatic fistulas)
Renal conditions (type 2 [proximal] renal tubular acidosis, toluene ingestion [late in the process of toluene intoxication], conditions associated with medications [ifosfamide, tenofovir, topiramate, carbonic anhydrase inhibitors such as acetazolamide])[3,41]
Decreased renal acid excretion
Early uremic acidosis
Type 1 renal tubular acidosis (e.g., due to amphotericin, lithium, Sjögren's syndrome)[3]
Type 4 renal tubular acidosis (hypoaldosteronism or pseudohypoaldosteronism)
Other causes: fluid resuscitation with saline, hyperalimentation (lysine, histidine, or arginine hydrochloride), administration of hydrochloride, ammonium chloride, cholestyramine, hippuric acid, sulfuric acid

* An anion gap of more than 10 mmol per liter above the upper limit of the reference value is highly suggestive of organic acidosis. A minor increase in the anion gap is less helpful in diagnosing metabolic acidosis.
† Advanced renal failure is indicated by a glomerular filtration rate below 20 ml per minute.

weak acid may account for up to 75% of the anion gap.[36,39,40] Without correction for hypoalbuminemia, the estimated anion gap does not reveal a clinically significant increase in anions (>5 mmol per liter) in more than 50% of cases. For every decrement of 1 g per deciliter in the serum albumin concentration, the calculated anion gap should be increased by approximately 2.3 to 2.5 mmol per liter.[9,36,39,40] Nevertheless, the albumin-corrected anion gap is merely an approximation, since it does not account for ions such as magnesium, calcium, and phosphate ions.

The anion gap can help to establish the diagnosis of diabetic ketoacidosis. In patients with this condition, the anion gap can be used to track the resolution of ketosis[9,15,23,33] and diagnose a normal anion-gap acidosis if large volumes of isotonic saline are administered.[50]

A high anion gap with a normal lactate level in a patient with alcoholism may be an important clue for the diagnosis of alcoholic ketoacidosis. This diagnosis may be missed because the test widely used to assess ketonuria (the nitroprusside test) reacts only with acetoacetate, not with β-hydroxybutyrate, the primary keto acid seen in alcoholic ketoacidosis. The pH may also be misleadingly normal or elevated because of concomitant metabolic alkalosis from vomiting or respiratory alkalosis from liver disease, pregnancy, high temperature, or sepsis.[18,51-53]

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The anion gap can also aid in the diagnosis of D-lactic acidosis in patients with the short-bowel syndrome, because the standard lactate level (L-lactate) remains normal while the anion gap increases.[49]

A low or negative anion gap is observed when hyperchloremia is caused by high levels of cations, as seen in lithium toxicity, monoclonal IgG gammopathy, or disorders characterized by high levels of calcium or magnesium. A negative anion gap is caused by pseudohyperchloremia in bromide or iodide intoxication.[33,36,54]

Normal Anion-Gap Acidosis

Chloride plays a central role in intracellular and extracellular acid–base regulation.[55] A normal anion-gap acidosis occurs when the decrease in bicarbonate ions corresponds with an increase in chloride ions to retain electroneutrality, which is also called hyperchloremic metabolic acidosis. This type of acidosis occurs from gastrointestinal loss of bicarbonate (e.g., because of diarrhea or ureteral diversion), from renal loss of bicarbonate that may occur in defective urinary acidification by the renal tubules (renal tubular acidosis), or in early renal failure when acid excretion is impaired.[12,56,57] Hospital-acquired hyperchloremic acidosis is usually caused by the infusion of large volumes of normal saline (0.9%).[58-67] Hyperchloremic acidosis should lead to increased renal excretion of ammonium, and measurement of urinary ammonium can therefore be used to differentiate between renal and extrarenal causes of normal anion-gap acidosis. However, since urinary ammonium is seldom measured, the urinary anion gap and urinary osmolal gap are often used as surrogate measures of excretion of urinary ammonium.[9,67]

The urinary anion gap ($[Na^+]+[K^+]-[Cl^-]$) is usually negative in normal anion-gap acidosis, but it will become positive when excretion of urinary ammonium (NH_4^+) (as ammonium chloride [NH_4Cl]) is impaired, as in renal failure, distal renal tubular acidosis, or hypoaldosteronism.[9,67] A negative urinary anion gap occurs in normal anion-gap acidosis because of diarrhea and proximal renal tubular acidosis, in which the distal acidification is intact.[56] The urinary anion gap becomes unreliable when polyuria is present, when the urine pH exceeds 6.5,[67] or when urinary ammonium is excreted with an anion other than chloride (e.g., keto acids, acetylsalicylic acid, D-lactic acid, and large quantities of penicillin).[9] Furthermore, the acidification of the urine requires adequate distal delivery of sodium; thus, the usefulness of the urinary anion gap is questionable when the urinary sodium level is less than 20 mmol per liter.[12] In such cases, the urinary osmolal gap is generally more reliable.

The urinary osmolal gap determines the difference between measured and calculated urinary osmolality. The urinary osmolality is calculated as follows:

$$(2\times[Na^+]+2\times[K^+])+(\text{urine urea nitrogen [in milligrams per deciliter]}\div 2.8)+(\text{urine glucose [in milligrams per deciliter]}\div 18)$$

or (in millimoles per liter):

$$(2\times[Na^+]+2\times[K^+])+(\text{urine urea nitrogen})+(\text{urine glucose}).$$

In patients without diabetes, the glucose concentration is often omitted from this calculation. A urinary osmolal gap below 40 mmol per liter in normal anion-gap acidosis indicates impairment in excretion of urinary ammonium. The urinary osmolal gap usually reflects the level of ammonium, except in the presence of large quantities of a nondissociated acid, such as β-hydroxybutyric acid in ketoacidosis. The urinary osmolal gap, as compared with the urinary anion gap, has a better correlation with the urinary ammonium value.[9,67]

METABOLIC ALKALOSIS

The normal kidney is highly efficient at excreting large amounts of bicarbonate and, accordingly, the generation of metabolic alkalosis (Fig. 2) requires both an increase in alkali and impairment in renal excretion of bicarbonate.[68-71] Loss of gastric fluid and the use of diuretics account for the majority of cases of metabolic alkalosis. By measuring chloride in urine, one can distinguish between chloride-responsive and chloride-resistant metabolic alkalosis. If the effective circulating volume is reduced, the kidneys avidly reabsorb filtered sodium, bicarbonate, and chloride, largely through activation of the renin–angiotensin–aldosterone system, thus reducing the concentration of urinary chloride.

A (spot sample) urinary chloride concentration of less than 25 mmol per liter suggests

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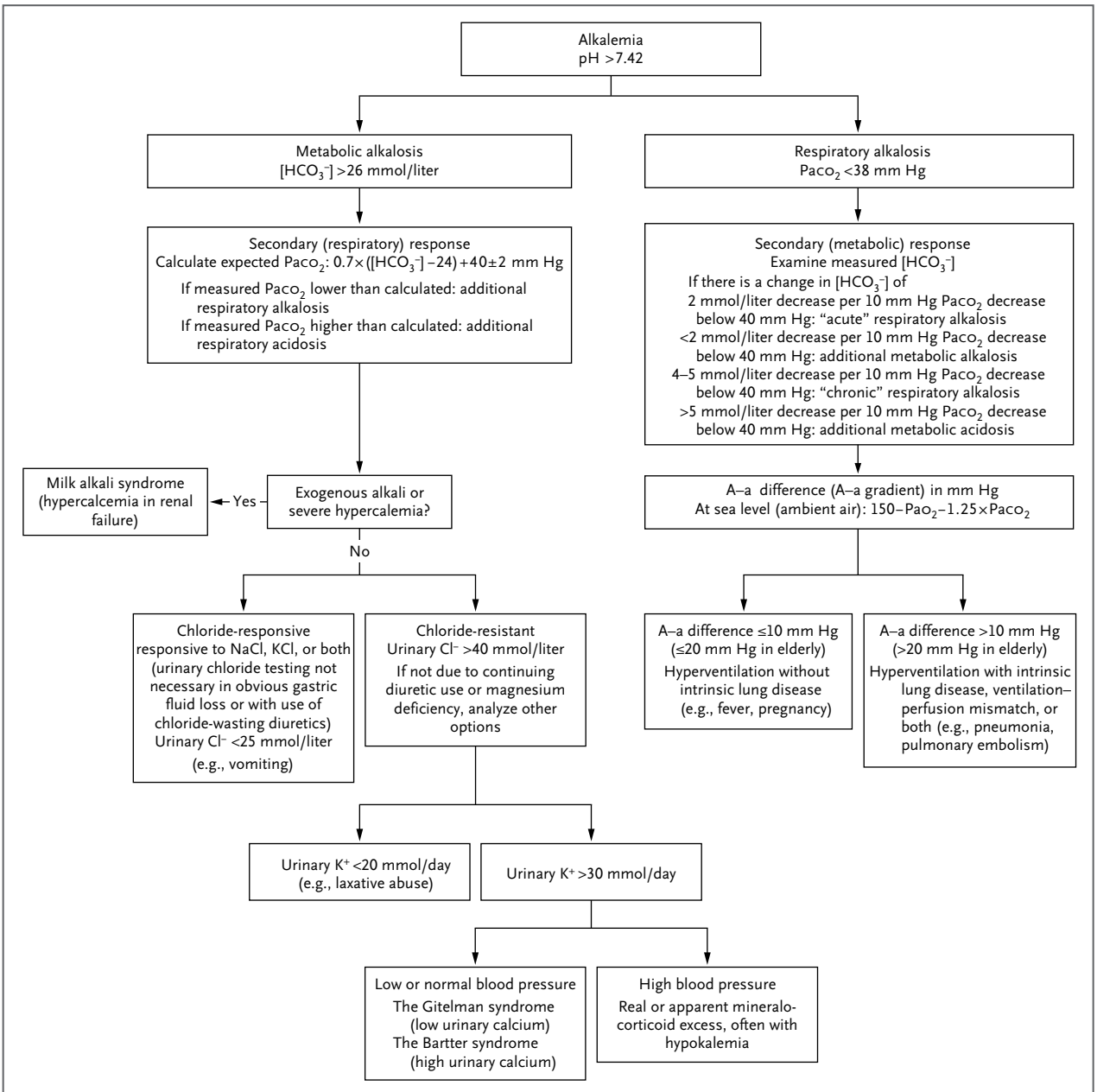

Figure 2. Assessment of Alkalosis.

Reference values for the alveolar–arterial (A–a) oxygen tension difference are less than 10 mm Hg in young persons and less than 20 mm Hg in the elderly. $Paco_2$ denotes partial pressure of arterial carbon dioxide (mm Hg), and Pao_2 partial pressure of arterial oxygen (mm Hg). To convert the values for $Paco_2$, Pao_2, and the alveolar–arterial difference to kilopascals, multiply by 0.1333.

chloride-responsive metabolic alkalosis. Administration of fluids with sodium chloride (usually with potassium chloride) restores effective arterial volume, replenishes potassium ions, or both with correction of metabolic alkalosis.

Metabolic alkalosis with a urinary chloride concentration of more than 40 mmol per liter is mainly caused by inappropriate renal excretion of sodium chloride, often reflecting mineralocorticoid excess or severe hypokalemia (potassi-

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um concentration <2 mmol per liter). The administration of sodium chloride does not correct this type of metabolic alkalosis, which, for that reason, is called "chloride-resistant." Diuretic-induced metabolic alkalosis is an exception because the concentration of chloride in urine may increase initially, until the diuretic effect wanes, after which the concentration will decrease to a level below 25 mmol per liter.[68-70] Other important causes of chloride-resistant metabolic alkalosis are the Bartter syndrome, the Gitelman syndrome, extreme hypercalcemia, and severe magnesium deficiency. In contrast to hyperaldosteronism, these causes are not associated with sodium retention (Fig. 2).

EVALUATION FOR THE PRESENCE OF MIXED METABOLIC ACID–BASE DISTURBANCES

The fourth step in the evaluation of acid–base disturbances is to consider the possibility of a mixed metabolic acid–base disturbance. In high anion-gap metabolic acidosis, the magnitude of the increase in the anion gap (the delta AG, or ΔAG) is related to the decrease in the bicarbonate ions ($\Delta[HCO_3^-]$). To diagnose a high anion-gap acidosis with concomitant metabolic alkalosis or normal anion-gap acidosis, the so-called delta-delta (Δ-Δ) may be used.[70,71] The delta gap is the comparison between the increase (delta) in the anion gap above the upper reference value (e.g., 12 mmol per liter) and the change (delta) in the concentration of bicarbonate ions from the lower reference value of bicarbonate ions (e.g., 24 mmol per liter).[9] In ketoacidosis, there is a 1:1 correlation between the increase in the anion gap and the decrease in the concentration of bicarbonate. In lactic acidosis, the decrease in the concentration of bicarbonate is 0.6 times the increase in the anion gap (e.g., if the anion gap increases by 10 mmol per liter, the concentration of bicarbonate should decrease by approximately 6.0 mmol per liter). This difference is probably due to the lower renal clearance of lactate as compared with keto-anions.[71] Hydrogen buffering in cells and bone takes time to reach completion. Accordingly, the ratio may be close to 1:1 with "very acute" lactic acidosis (e.g., shortly after seizures or in persons who exercise to the point of exhaustion).[71] If $\Delta AG - \Delta[HCO_3^-] = 0 \pm 5$ mmol per liter in a patient with ketoacidosis or if $0.6\ \Delta AG - \Delta[HCO_3^-] = 0 \pm 5$ mmol per liter in a patient with lactic acidosis, simple anion-gap metabolic acidosis is present. A difference greater than 5 mmol per liter suggests a concomitant metabolic alkalosis, and if the difference is less than −5 mmol per liter, a concomitant normal anion-gap metabolic acidosis is diagnosed.

In certain cases, normal values for concentrations of bicarbonate, P_{aCO_2}, and pH do not ensure the absence of an acid–base disturbance. An increase in the anion gap of more than 5 mmol per liter may then be the only clue to an underlying mixed acid–base disorder.[9,71] Because the individual anion gap and concentration of bicarbonate before the acid–base disorder are usually not known, and the ranges of normal values for the anion gap and the concentration of bicarbonate are wide, the $\Delta AG - \Delta[HCO_3^-]$ remains an approximation.[70,71]

CONSIDERATION OF THE SERUM (OR PLASMA) OSMOLAL GAP

The fifth step in the evaluation of an acid–base disturbance is to note the serum osmolal gap in any patient with an unexplained high anion-gap acidosis, coma, or suspicion of ingestion of a (toxic) alcohol and in hospitalized patients with an increased risk of iatrogenic propylene glycol intoxication (e.g., because of high-dose lorazepam administration in sedated patients in an intensive care unit).[72-76] Laboratory confirmation of toxic alcohol ingestion is generally not rapidly available, and physicians must infer such a diagnosis by considering disorders that may necessitate immediate treatment. The osmolal gap is the difference between measured serum osmolality and calculated serum osmolality. The serum osmolality is calculated as

$$2 \times ([Na^+]\ \text{[in millimoles per liter]}) + (\text{glucose [in milligrams per deciliter]}) \div 18 + (\text{BUN [in milligrams per deciliter]}) \div 2.8.$$

If ethanol is involved, the result of this calculation would be added to the amount of ethanol (in milligrams per deciliter) divided by 3.7. An osmolal gap below 10 mOsm per kilogram is considered to be normal, but the normal range in the general population is large (–10 to 10 mOsm per

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Table 3. Common Medical Conditions Characterized by Respiratory Acidosis and Alkalosis.*

Type of Acidosis	Common Medical Conditions
Respiratory acidosis	
Acute	
Normal alveolar–arterial O_2 difference	Depression of the central respiratory center by cerebral disease (encephalitis or trauma) or drugs (narcotics, barbiturates, or benzodiazepines)
High alveolar–arterial O_2 difference†	Airway obstruction related to acute exacerbations of asthma or pneumonia
Chronic	
Normal alveolar–arterial O_2 difference	Neuromuscular disease (e.g., myasthenia gravis, amyotrophic lateral sclerosis, Guillain–Barré syndrome, or muscular dystrophy), kyphoscoliosis
High alveolar–arterial O_2 difference†	Chronic obstructive pulmonary disease
Respiratory alkalosis	
Acute	
Normal alveolar–arterial O_2 difference	Pain, anxiety, fever, stroke, meningitis, trauma, severe anemia, salicylate toxicity
High alveolar–arterial O_2 difference†	Pneumonia, pulmonary edema, pulmonary embolism, aspiration, congestive heart failure, sepsis
Chronic	
Normal alveolar–arterial O_2 difference	Pregnancy, hyperthyroidism, hepatic failure
High alveolar–arterial O_2 difference†	Pulmonary embolism in pregnancy, liver failure with aspiration pneumonia

* The alveolar–arterial O_2 difference increases with age. For every decade a person has lived, the alveolar–arterial difference is expected to increase by 2 mm Hg; alternatively, one can compensate for age using the following formula: (alveolar–arterial O_2 difference = $[\frac{Age}{4} + 4]$).
† Minor defects may result in a normal alveolar–arterial O_2 difference.

liter).[73,74] In ethylene glycol and methanol intoxication, the osmolal gap will be high shortly after ingestion, but substantial amounts of acids will not be generated for several hours.[72-76] Symptoms are considerably delayed by simultaneous ethanol ingestion because of competition for the enzyme alcohol dehydrogenase.[74-76]

The use of the osmolal gap has some pitfalls. The wide normal range of the osmolal gap in the general population renders the test rather insensitive to small but potentially toxic concentrations of ethylene glycol and methanol.[74] In addition, the osmolal gap lacks specificity, given that it may also be moderately elevated in other clinical situations such as lactic acidosis, alcoholic ketoacidosis, and diabetic ketoacidosis.[74]

EVALUATION OF THE RESPIRATORY COMPONENT OF AN ACID–BASE DISORDER

The respiratory component of an acid–base disorder can be determined by differentiating between acute and chronic respiratory acid–base disorders with the use of clinical information and calculations (Table 1) and the oxygenation level. Hypoxemia, a major cause of lactic acidosis, may induce respiratory alkalosis. Evaluation of the partial pressure of arterial oxygen (Pao_2) relative to ventilation, with the alveolar–arterial oxygen-tension difference (hereafter called the alveolar–arterial difference) taken into account, may distinguish pulmonary from extrapulmonary diseases. The difference in the partial oxygen pressures between the alveolar and arterial side of the alveolar–capillary membrane will be high if the patient has associated lung disease (Table 3).[77,78] The Pao_2 in the alveolus is not equal to that in the pulmonary circulation because physiological hypoventilation occurs in various portions of the lung; therefore, the alveolar–arterial difference will be about 5 to 10 mm Hg in healthy young persons and 15 to 20 mm Hg in healthy elderly persons. The alveolar–arterial difference is calculated as

$$Fio_2 \times (\text{barometric pressure} - \text{water-vapor pressure}) - Pao_2 - (Paco_2 \div \text{gas-exchange ratio}).$$

The fraction of inspired oxygen (Fio_2) is 0.21 in ambient air, the barometric pressure is 760 mm Hg at sea level, and the water-vapor pressure is 47 mm Hg at 37°C. The gas-exchange ratio, which is approximately 0.8 at steady-state levels, varies according to the relative utilization of carbohydrate, protein, and fat. At sea level and a body temperature of 37°C, the alveolar–arterial difference can be estimated[77,78] as

$$Fio_2 \times (760 - 47) - Pao_2 - (Paco_2 \div 0.8)$$

or

$$150 - Pao_2 - 1.25\ Paco_2.$$

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INTERPRETATION OF ACID–BASE DISORDERS IN THE CLINICAL CONTEXT

The final step in evaluating acid–base disorders is to determine the cause of the identified processes. The evaluation of the laboratory data must fit with the clinical presentation of the patient (see box). The stepwise approach described here can be helpful in assessing acid–base disorders, but one should always check for other information to support the diagnosis, such as a lactate gap in ethylene glycol intoxication[79] (see the Supplementary Appendix, available with the full text of this article at NEJM.org) or an oxygen-saturation gap in carbon monoxide, methemoglobinemia, or cyanide intoxication.[80]

CONCLUSIONS

Currently, there is no ideal method of assessing acid–base disturbances. The two other widely practiced methods also have limitations. The physicochemical (strong ion or Stewart[22,57,81])

Three Case Examples

Patient 1, a 22-year-old woman who had been injured in an accident, received 6 liters of isotonic saline, after which the level of sodium was 135 mmol per liter, potassium 3.8 mmol per liter, chloride 115 mmol per liter, and bicarbonate 18 mmol per liter. The arterial blood pH was 7.28, and the $Paco_2$ was 39 mm Hg. The urinary sodium level was 65 mmol per liter, potassium 15 mmol per liter, and chloride 110 mmol per liter.

This patient had a low anion-gap metabolic acidosis (2 mmol per liter), but she also had respiratory acidosis, because the expected $Paco_2$ is lower ($1.5 \times$ bicarbonate $+ 8 \pm 2$ mm Hg $=$ 35 ± 2 mm Hg). If these findings are the result of chest-wall expansion problem such as rib fractures, the alveolar–arterial O_2 difference could be normal, assuming no underlying lung pathology. The majority of patients with a normal anion-gap metabolic acidosis have diarrhea and renal tubular acidosis. The high chloride content of saline normalizes the anion gap because of the concomitant decrease in the level of bicarbonate. The low anion gap is probably the result of a low albumin level because of bleeding and dilution. The urinary anion gap ($[Na^+]+[K^+]-[Cl^-]$) was negative (–30 mmol per liter) because of the use of saline. It would have been positive in a patient with renal tubular acidosis type 1 or 4.

Patient 2, a 50-year-old woman with a recent onset of hypertension, the level of sodium was 150 mmol per liter, potassium 2.2 mmol per liter, chloride 103 mmol per liter, and bicarbonate 32 mmol per liter. The arterial blood pH was 7.50, and the $Paco_2$ was 43 mm Hg.

This patient was found to have an aldosterone-secreting adrenal adenoma. In a patient with metabolic alkalosis and hypokalemia, the clinician should always rule out vomiting and the use of diuretics before considering a renin–aldosterone problem. Vomiting should lead to a chloride level below 10 mmol per liter in the urine, whereas an aldosterone-secreting tumor should lead to a urinary chloride level greater than 40 mmol per liter.[63] The expected $Paco_2$ would be $40 + 0.7 \times \Delta$bicarbonate ions $= 40 + 0.7 \times (32 - 24) = 45.7$ mm Hg, which is only marginally higher than the value in the patient.

Patient 3, a previously healthy 22-year-old man, developed large volumes of watery diarrhea from infectious gastroenteritis. Laboratory tests revealed a plasma sodium concentration of 140 mmol per liter, potassium 3.0 mmol per liter, chloride 86 mmol per liter, and bicarbonate 38 mmol per liter. The arterial blood pH was 7.60, and the $Paco_2$ was 40 mm Hg.

The patient had metabolic alkalosis. The levels of pH and bicarbonate increased, but because the $Paco_2$ did not increase, the patient also had respiratory alkalosis, perhaps because of stress or fever. The albumin-uncorrected anion gap was 16 mmol per liter; a much higher value might be indicative of additional metabolic acidosis. Also, metabolic alkalosis, particularly that which is caused by vomiting or diuretic use, can be associated with an increment in the serum anion gap of approximately 4 to 6 mmol per liter because of an increase of the albumin concentration and its release of protons.[33] The metabolic alkalosis was the result of gastrointestinal losses.

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approach is complex and often requires cumbersome calculations that cannot be performed at the bedside. Many clinicians think that it does not provide a diagnostic or prognostic advantage[33,42,81] and that the large number of parameters used in calculations will increase the magnitude of variability and error.[26] The standard base-excess method accurately quantifies the change in metabolic acid–base status in vivo and is conveniently provided by the blood-gas machine.[82] However, "mixed" acid–base disorders will not be detected[42] by that method without the use of elaborate base-excess partitioning.[34,52,53] Therefore, in our view, the physiological approach, considered here, remains the simplest, most rigorous, and most serviceable approach to the assessment of acid–base disorders.[42]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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